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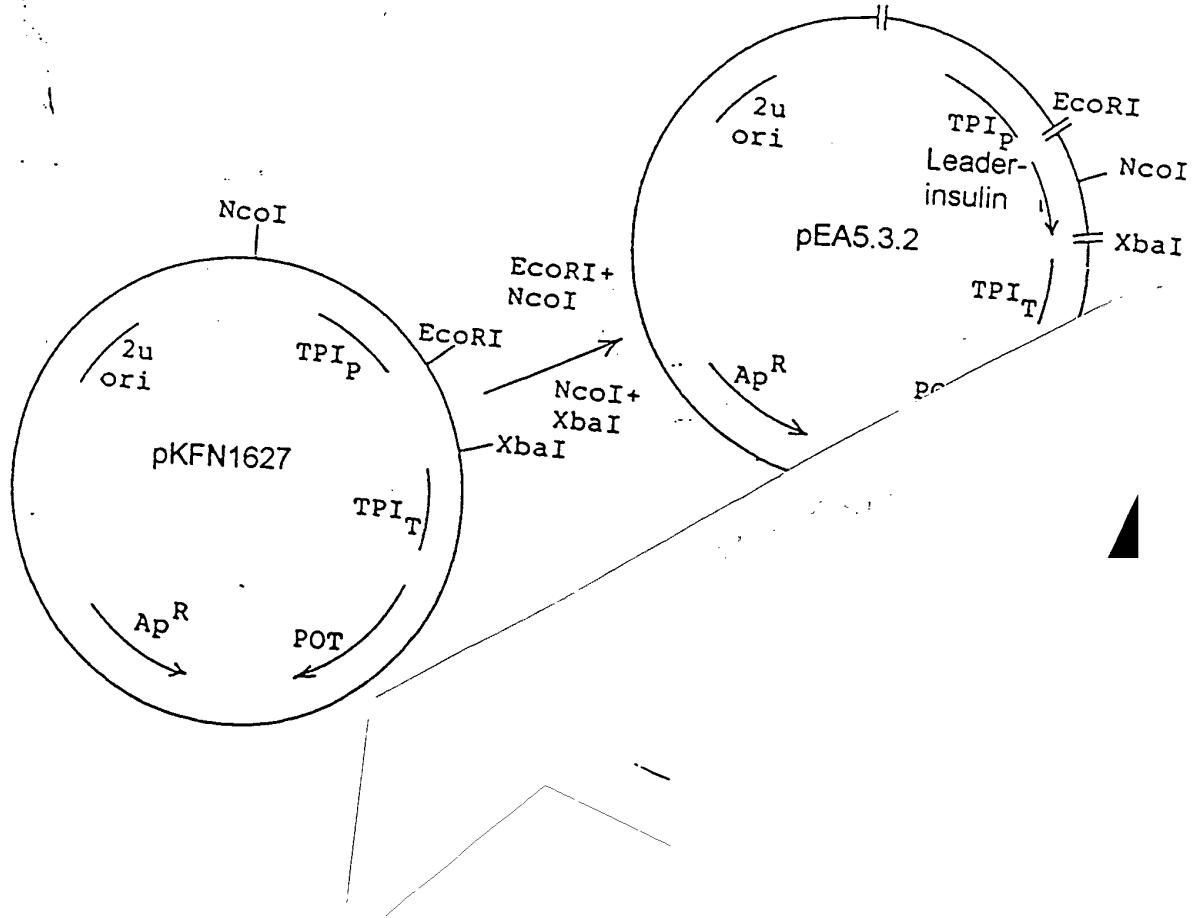
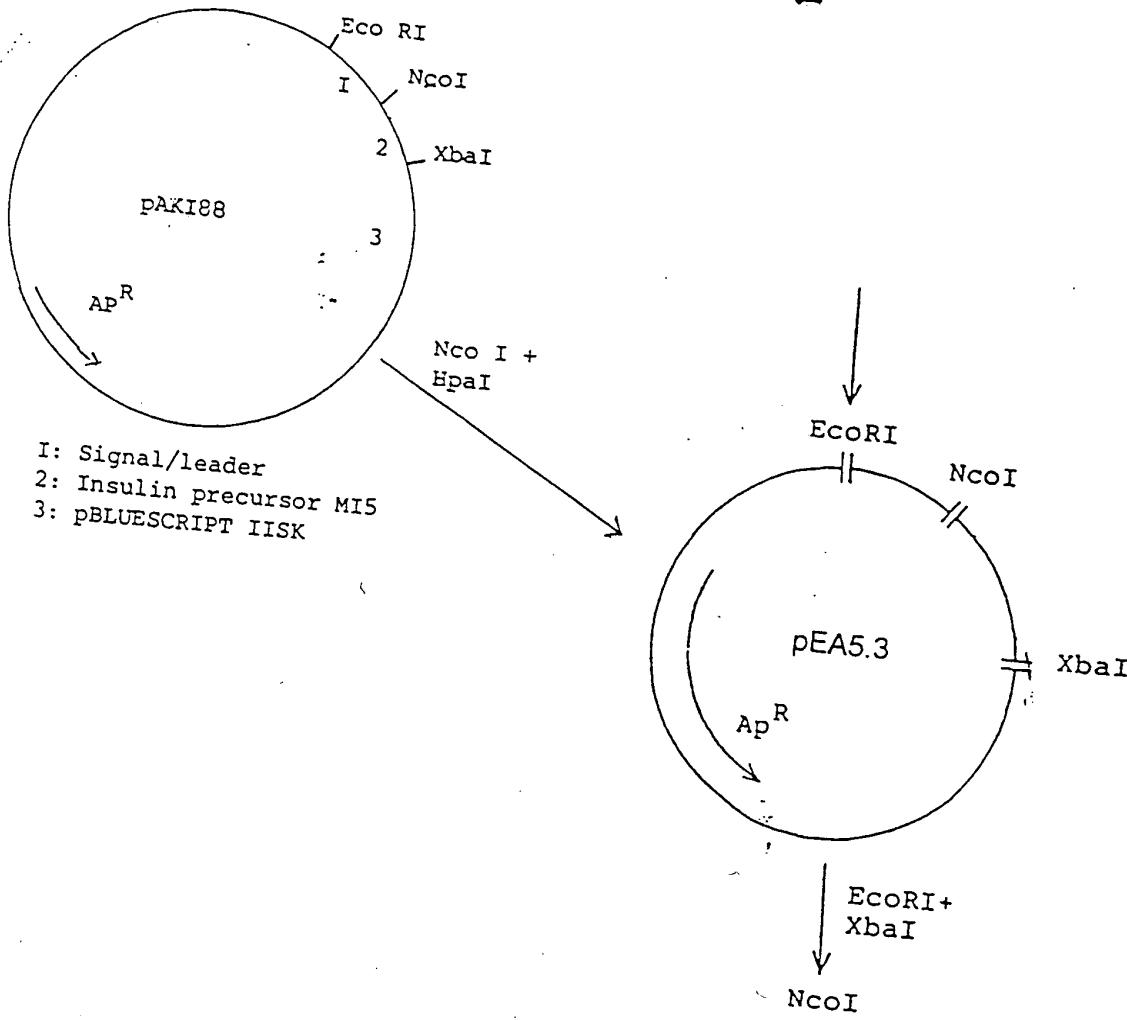
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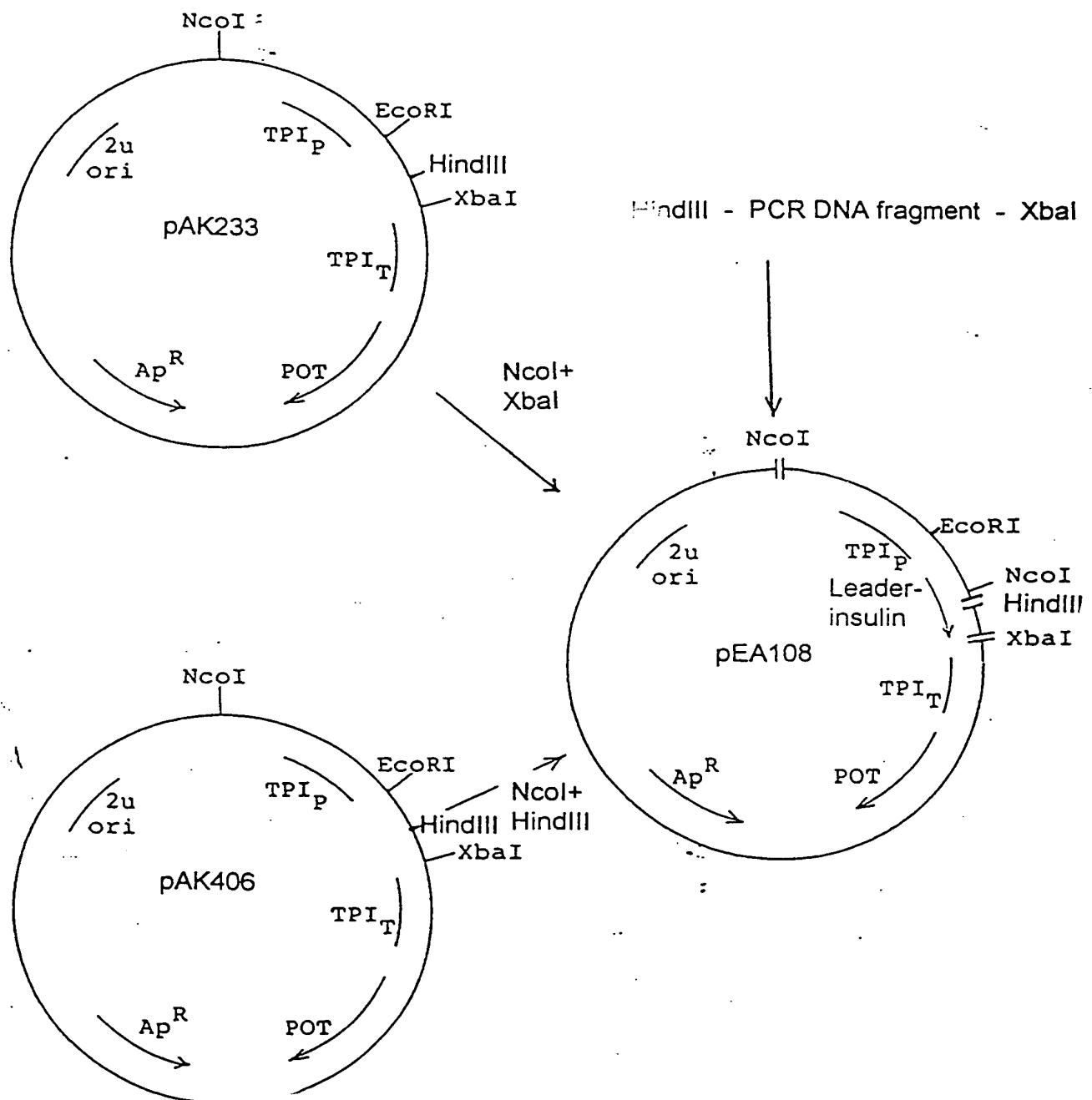
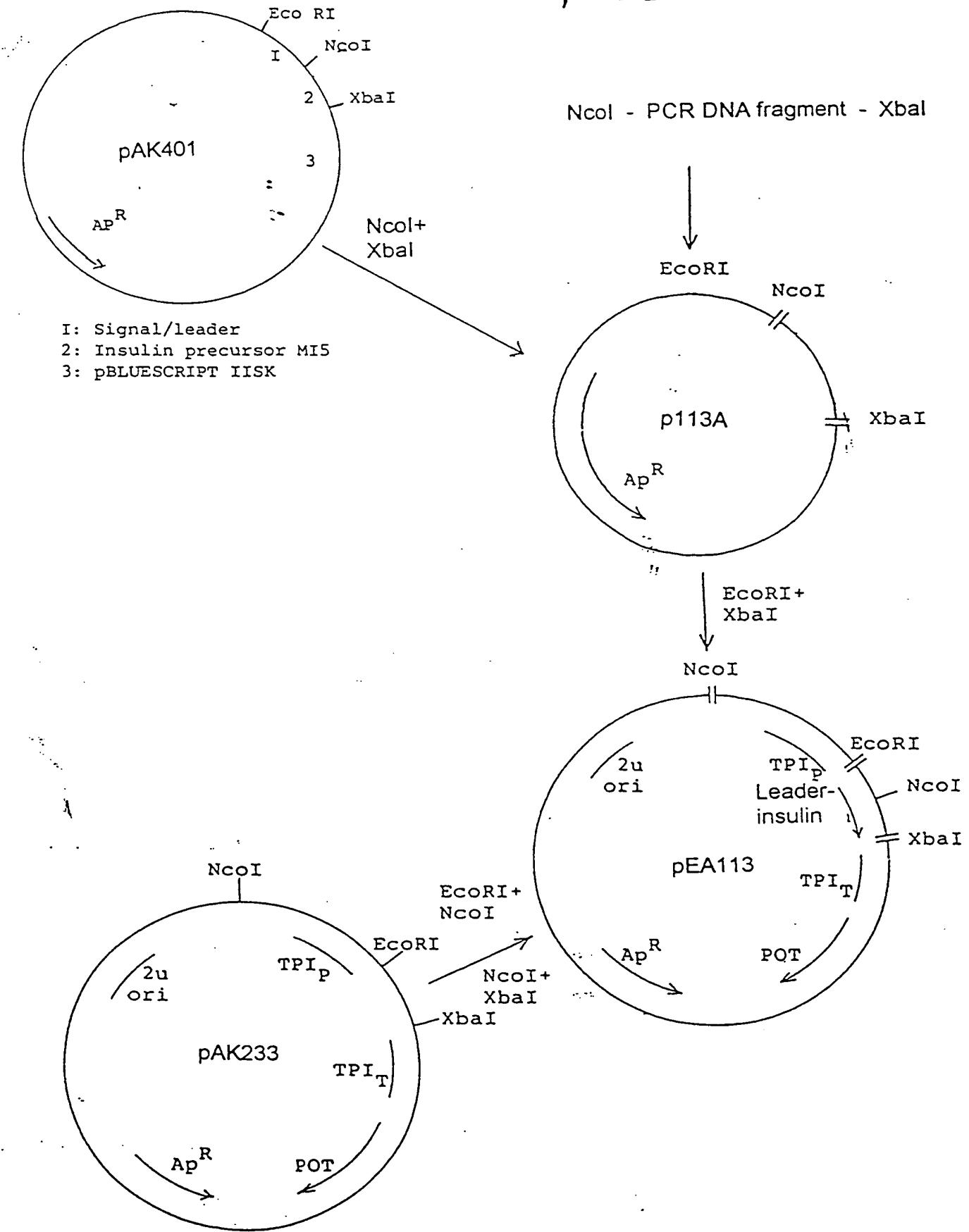


Fig 3



human insulin
LaC212spx3 Leader-MI5
B(1-29) SDDAK A(1-21)

Figure 4

ATCGAATTCCATTCAAGAACAAAGATTACAAACTATCAATTCATAACAC
1 -----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGACCAAAAGAACATGAAGGCTGTTCTGGTTTGTCCTGATCGGATTCTG
61 -----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTGGTTCTTACTTCCGACAAAAGAACCAAAACAGGAACCTAGCCTAAGAC
I * T T K R M K A V F L V L S L I G F C -
CTGGGCCAACCAACCAGTCACTGGCGATGAATCATCTGTTGAGATTCCGGAAGAGTCTCTGAT
121 -----+-----+-----+-----+-----+-----+-----+ 180
GACCCGGGTTGGTCAGTGACCGCTACTTAGACAACTCTAAGGCCTCTCAGAGACTA
W A Q P V T G D E S S V E I P E E S L I -
CATCGCTAAAAACACCACTTGGCTAACGTCGCCATGGCTAACAGAGATTGTTAACCAACA
181 -----+-----+-----+-----+-----+-----+-----+ 240
GTAGCGACTTTGTTGAAACCGATTGCAGCGGTACCGATTCTCTAACGAAATTGGTTGT
I A E N T T L A N V A M A K R F V N Q H -
CTTGTGCGGTTCTCACTTGGTTGAAGCTTGACTTGGTTGTTGAAAGAGGTTCTT
241 -----+-----+-----+-----+-----+-----+-----+ 300
GAACACGCCAACAGAGTGAACCAACTCGAACATGAACCAAACACCACCTTCTCCAAAGAA
L C G S H L V E A L Y L V C G E R G F -
CTACACTCCAAAGTCTGACGACGCTAACGGGTATCGTTAACATGTTGACTTCTATC
301 -----+-----+-----+-----+-----+-----+-----+ 360
GATGTGAGGTTTCAGACTGCTGCGATTCCCAGAACATGAACTTGTACAAACATGAAGATAGAC
Y T P K S D D A K G I V E Q C C T S I C -
TTCTTTGTACCAATTGGAAAACACTACTGTAACTAGACGCAGCCCCCAGGCTCTAGA
361 -----+-----+-----+-----+-----+-----+-----+ 415
AAGAAACATGGTTAACCTTGATGACATTGATCTGCGTCGGCGTCCGAGATCT
S L Y Q L E N Y C N * T Q P A G S R -

human insulin
MFalpha1 leader-MI5
B(1-29) SDDAK A(1-21)
B1-Glu, B28-Glu

Figure 5

ATCGAATTCCATTCAAGAACAGAAGATTACAAACTATCAATTCATACAC
1 -----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAAGTTCTTATCAAGTTGTTCTTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAAACGATTAAAAGAATGAGATTCCTCAATTCTACTGCAGTTTATTGCAGC
61 -----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTAATTCTACTCTAAAGGAAGTTAAAATGACGTAAAATAAGCGTCG
I * T I K R M R F P S I F T A V L F A A -
ATCCTCCGCATTAGCTGCTCCAGTCACACTACAACAGAAGATGAAACGGCACAAATTCC
121 -----+-----+-----+-----+-----+-----+-----+ 180
TAGGAGGCGTAATCGACGAGGTCAAGTTGATGTTCTACTTTGCCGTGTTAAGG
S S A L A A P V N T T T E D E T A Q I P -
GGCTGAAGCTGTCATCGTTACTCAGATTAGAAGGGGATTCGATGTTGCTGTTGCC
181 -----+-----+-----+-----+-----+-----+-----+ 240
CCGACTTCGACAGTAGCCAATGAGTCTAAATCTCCCCCTAAAGCTACAAACGACAAACGG
A E A V I G Y S D L E G D F D V A V L P -
ATTTCCAACAGCACAAATAACGGTTATTGTTATAAAATACTACTATTGCCAGCATTGC
241 -----+-----+-----+-----+-----+-----+-----+ 300
TAAAAGGTTGTCGTGTTATTGCCAATAACAAATATTATGATGATAACGGTCGTAACG
F S N S T N N G L L F I N T T I A S I A -
TGCTAAAGAAGAAGGGTATCTTGGATAAGAGAGAAGTTAACCAACACTGTGCGGTTC
301 -----+-----+-----+-----+-----+-----+-----+ 360
ACGATTCTTCTTCCCCATAGAACCTATTCTCTCTCAATTGGTTGTGAACACGCCAAG
A K E E G V S L D K R E V N Q H L C G S -
TCACTTGGTTGAAGCTTGACTTGGTTGTTGAAAGAGGTTCTTCTACACTGAAAA
361 -----+-----+-----+-----+-----+-----+-----+ 420
AGTGAACCAACTTCGAAACATGAACCAAACACCACCTTCTCCAAAGAAGATGTGACTTTT
H L V E A L Y L V C G E R G F F Y T E K -
GTCTGACGACGCTAAGGGTATCGTTGAACAATGTTGACTTCTATCTGTTCTTGTACCA
421 -----+-----+-----+-----+-----+-----+-----+ 480
CAGACTGCTGCGATTCCCATAGCAACTGTTACAACATGAAGATAGACAAGAAACATGGT
S D D A K G I V E Q C C T S I C S L Y Q -
ATTGGAAAACACTGTAACTAGACGCAGCCCGCAGGCTCTAGA
481 -----+-----+-----+-----+-----+-----+ 523
TAAACCTTTGATGACATTGATCTGCGTCGGCGTCCGAGATCT
L E N Y C N * T Q P A G S R -

human insulin
LaC212spx3 Leader-MI5
B(1-29) SDDAK A(1-21)
A21-Ala, B3-Asp

Figure 6

ATCGAATTCCATTCAAGAATAGTTCAAACAAGAAGATTACAAACTATCAATTCATAACAC
1 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTTCTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGACCAAAAGAATGAAGGCTGTTCTGGTTTGTCCTGATCGGATTCTG
61 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTGGTTCTTACTTCCGACAAAAGAACCAAAACAGGAACCTAGCCTAAGAC
I * T T K R M K A V F L V L S I G F C -
CTGGGCCAACCAACAGTCACTGGCGATGAATCATCTGTTGAGATTCCG AAGAGTCTCTGAT
121 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 180
GACCCGGGTTGGTCAGTGACCGCTACTTAGACAACTCTAAGGCCTCTCAGAGACTA
W A Q P V T G D E S S V E I P E E S L I -
CATCGCTAAAACACCACTTGGCTAACGTGCCATGGCTAAGAGATTGTTGACCAACA
181 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 240
GTAGCGACTTTGTTGAAACCGATTGCAGCGGTACCGATTCTCTAAGCAACTGGTTGT
I A E N T T L A N V A M A K R F V D Q H -
CTTGTGCGGTTCTCACTTGGTTGAAGCTTGACTTGGTTGTTGAAAGAGGTTCTT
241 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 300
GAACACGCCAAGAGTGAACCAACTTCGAAACATGAACCAAAACACCACCTTCTCCAAAGAA
L C G S H L V E A L Y L V C G E R G F F -
CTACACTCCAAAGTCTGACGACGCTAACGGTATCGTTGAACAAATGTTGACTTCTATCTG
301 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 360
GATGTGAGGTTTCAGACTGCTGCGATTCCCAGCAACTGTTACAACATGAAGATAGAC
Y T P K S D D A K G I V E Q C C T S I C -
TTCTTTGTACCAATTGGAAAACTACTGTGCTTAGACGCAGCCCCCAGGCTCTAGA
361 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 415
AAGAAACATGGTTAACCTTTGATGACACGAATCTGCGTCGGCGTCCGAGATCT
S L Y Q L E N Y C A * T Q P A G S R -

human insulin
LaC212spx3 Leader-MI5
B(1-29) SDDAK A(1-21)
A21-Ala, B3-Thr

Figure 7

ATCGAATTCCATTCAAGAACAGATTACAAACTATCAATTACAC
1 -----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTTCTAATGTTGATAGTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGACCAAAAGAACATGAAGGCTGTTCTGGTTTCGATCGGATTCTG
61 -----+-----+-----+-----+-----+-----+ 120
TTATATTGCTGGTTCTTACTTCCGACAAAAGAACCAACAGGAACCTAGCCTAAGAC
I * T T K R M K A V F L V L S L I G F C -
CTGGGCCAACAGTCACTGGCGATGAATCATCTGTTGAGATTCCGGAAGAGTCTCTGAT
121 -----+-----+-----+-----+-----+-----+ 180
GACCCGGGTTGGTCAGTGACCGCTACTTAGACAACTCTAAGGCCTCTCAGAGACTA
W A Q P V T G D E S S V E I P E E S L I -
CATCGCTGAAAACACCACTTGGCTAACGTGCCATGGCTAACAGAGATTGTTACTCAACA
181 -----+-----+-----+-----+-----+-----+ 240
GTAGCGACTTTGGTGAACCGATTGCAGCGTACCGATTCTCTAAGCAATGAGTTGT
I A E N T T L A N V A M A K R F V T Q H -
CTTGTGCGGTTCTCACTTGGTTGAAGCTTGACTTGGTTGGTGAAGAGGTTCTT
241 -----+-----+-----+-----+-----+-----+ 300
GAACACGCCAACAGACTGAACCAACTTCGAAACATGAACCAACACCACCTTCTCAAAGAA
L C G S H L V E A L Y L V C G E R G F F -
CTACACTCCAAAGTCTGACGACGCTAACGGGTATCGTTGAACAAATGTTGACTTCTATCTG
301 -----+-----+-----+-----+-----+-----+ 360
GATGTGAGGTTTCAGACTGCTGCGATTCCCAGCAACTGTTACAACATGAAGATAGAC
Y T P K S D D A K G I V E Q C C T S I C -
TTCTTTGTACCAATTGGAAAACACTGTGCTTAGACGCCAGCCGCAGGCTCTAGA
361 -----+-----+-----+-----+-----+-----+ 415
AAGAAACATGGTTAACCTTTGATGACACGAATCTGCGTCGGCGTCCGAGATCT
S L Y Q L E N Y C A * T Q P A G S R -

human insulin
LaC?12spx3 Leader-MI5
B(1-29) SDDAK A(1-21)
A21-Gly, B3-Asp

Figure 8

ATCGAATTCCATTCAAGAATAGTTCAAACAAAGAAGATTACAAACTATCAATTCATAACAC
1 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGACCAAAAGAACATGAAGGCTGTTTCTTGGTTTGTCCTGATCGGATTCTG
61 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTGGTTCTTACTTCCGACAAAAGAACCAAAACAGGAACCTAGCCTAAGAC
I * T T K R M K A V F L V L S L I G F C -
CTGGGCCAACAGTCACTGGCGATGAATCATCTGTTGAGATTCCGGAAAGAGTCTCTGAT
121 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 180
GACCCGGGTTGGTCAGTGACCGCTACTTAGTACACAACCTCTAAGGCCTCTCAGAGACTA
W A Q P V T G D E S S V E I P E E S L I -
CATCGCTGAAAACACCACTTGGCTAACGTGCCATGGCTAACAGAGATTGTTGACCAACA
181 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 240
GTAGCGACTTTGTTGAAACCGATTGCAGCGGTACCGATTCTCTAAGCAACTGGTTGT
I A E N T T L A N V A M A K R F V D Q H -
CTTGTGCGGTTCTCACTTGGTTGAAGCTTGACTTGGTTGAAAGAGGTTCTT
241 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 300
GAACACGCCAACAGAGTGAACCAACTCGAAACATGAACCAAAACACCACCTTCTCCAAAGAA
L C G S H L V E A L Y L V C G E R G F F -
CTACACTCCAAAGTCTGACGACGCTAACGGGTATCGTTAACAAATGTTGACTTCTATCTG
301 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 360
GATGTGAGGTTTCAGACTGCTCGATTCCCATAGCAACTGTTACAACATGAAGATAGAC
Y T P K S D D A K G I V E Q C C T S I C -
TTCTTTGTACCAATTGGAAAACACTACTGTGGTTAGACGCAGCCCGCAGGCTCTAGA
361 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 415
AAGAAAACATGGTTAACCTTTGATGACACCAATCTGCGTCGGCGTCCGAGATCT
S L Y Q L E N Y C G * T Q P A G S R -

human insulin
LaC212spx3 Leader-MI5
B(1-29) SDDAK A(1-21)
A21-Gly, B3-Thr

Figure 9

ATCGAATTCCATTCAAGAATAGTTCAAACAAGAAGATTACAAACTATCAATTACAC
1 -----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGACCAAAAGAACATGAAGGCTGTTCTGGTTTGCCTGATCGGATTCTG
61 -----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTGGTTCTTACTTCCGACAAAAGAACCAAAACAGGAACCTAGCCTAACAGAC
I * T T K R M K A V F L V L S L I G F C -
CTGGGCCAACCAGTCACTGGCGATGAATCATCTGTTGAGATTCCGGAAAGAGTCTCTGAT
121 -----+-----+-----+-----+-----+-----+-----+ 180
GACCCGGGTTGGTCAGTGACCGCTACTTAGACAACTCTAAGGCCTCTCAGAGACTA
W A Q P V T G D E S S V E I P E E S L I -
CATCGCTAAAACACCACTTGGCTAACGTGCCATGGCTAACAGAGATTGTTACTCAACA
181 -----+-----+-----+-----+-----+-----+-----+ 240
GTAGCGACTTTGTTGAAACCGATTGACGGTACCGATTCTCTAACAGCAATGAGTTGT
I A E N T T L A N V A M A K R F V T Q H -
CTTGTGCGGTTCTCACTTGGTTGAAGCTTGTACTTGGTTGTTGAAAGAGGTTCTT
241 -----+-----+-----+-----+-----+-----+-----+ 300
GAACACGCCAACAGAGTGAACCAACTTCGAAACATGAACCAAAACACCACCTTCTCCAAAGAA
L C G S H L V E A L Y L V C G E R G F F -
CTACACTCCAAAGTCTGACGACGCTAACGGGTATCGTTAACAAATGTTGACTTCTATCTG
301 -----+-----+-----+-----+-----+-----+-----+ 360
GATGTGAGGTTTCAGACTGCTGCGATTCCCAGCAACTGTTACAACATGAAGATAGAC
Y T P K S D D A K G I V E Q C C T S I C -
TTCTTTGTACCAATTGGAAAACACTGTGGTTAGACGCAGCCCCCAGGCTCTAGA
361 -----+-----+-----+-----+-----+-----+-----+ 415
AAGAAACATGGTTAACCTTTGATGACACCAATCTGCGTCGGCGTCCGAGATCT
S L Y Q L E N Y C G * T Q P A G S R -

human insulin
MFalpha1 leader-MI5
B(1-29) SDDAK A(1-21)

Figure 10

ATCGAATTCCATTCAAGAACAGAAGATTACAAACTATCAATTCATACAC
1 -----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGATTAAGAACGATGAGATTCCCTCAATTTCAGTTACTGCAGTTATTGCAGC
61 -----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTAATTTCCTTACTCTAAAGGAAGTTAAAATGACGTCAAATAAGCGTCG
I * T I K R M R F P S . I F T A V L F A A -
ATCCTCCGCATTAGCTGCTCCAGTCACACTACAAACAGAACAGATGAAACGGCACAAATTCC
121 -----+-----+-----+-----+-----+-----+-----+ 180
TAGGAGGCGTAATCGACGAGGTCAGTTGTATGTTCTACTTGCCGTGTTAAGG
S S A L A A P V N T T T E D E T A Q I P -
GGCTGAAGCTGTCATCGGTTACTCAGATTTAGAAGGGGATTCGATGTTGCTGTTGCC
181 -----+-----+-----+-----+-----+-----+-----+ 240
CCGACTTCGACAGTAGCCAATGAGTCTAAATCTCCCCAAAGCTACAACGACAAAACGG
A E A V I G Y S D L E G D F D V A V L P -
ATTTCACAGCACAAATAACGGGTATTGTTATAAAATACTACTATTGCCAGCATTGC
241 -----+-----+-----+-----+-----+-----+-----+ 300
TAAAAGGTTGTCGTGTTATTGCCAATAACAAATATTATGATGATAACGGTCGTAACG
F S N S T N N G L L F I N T T I A S I A -
TGCTAAAGAAGAAGGGTATCTTGGATAAGAGATTGTTAACCAACACTTGTGCGGTTTC
301 -----+-----+-----+-----+-----+-----+-----+ 360
ACGATTCTTCTTCCCCATAGAAACCTATTCTCTAACGAAATTGGTTGTAAACACGCCAAG
A K E E G V S L D K R F V N Q H L C G S -
TCACTTGGTTGAAGCTTGTACTTGGTTGTGGTAAAGAGGTTCTTCTACACTCCAAA
361 -----+-----+-----+-----+-----+-----+-----+ 420
AGTGAACCAACTTCGAAACATGAACCAACACCCTTCTCCAAAGAAGATGTGAGGTT
H L V E A L Y L V C G E R G F F Y T P K -
GTCTGACGACGCTAAGGTATCGTTGAACAATGTTGACTTCTATCTGTTCTTGTACCA
421 -----+-----+-----+-----+-----+-----+-----+ 480
CAGACTGCTGCGATTCCCATAGCAACTTGTACAACATGAAGATAGACAAGAAACATGGT
S D D A K G I V E Q C C T S I C S L Y Q -
ATTGGAAAACACTGTAACTAGACGCAGCCGCAGGCTCTAGA
481 -----+-----+-----+-----+-----+-----+ 523
TAAACCTTTGATGACATTGATCTGCGTCGGCGTCCGAGATCT
L E N Y C N * T Q P A G S R -

human insulin
LaC212spx3 Leader - insulin
B(1-29) EKR A(1-21)
A21-Gly

Figure 11

ATCGAATTCCATTCAAGAATAGTTCAAACAAGAAGATTACAAACTATCAATTCATAACAC
1 -----+-----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTTCTTATCAAGTTGTTCTCTAATGTTGATAGTTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGACCAAAAGAATGAAGGCTGTTCTGGTTTGTCTGATCGGATTCTG
61 -----+-----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTGGTTCTTACTTCCGACAAAAGAACCAACAGGAACTAGCCTAAGAC
I * T T K R M K A V F L V L S L I G F C -
CTGGGCCAACCAACCAGTCACTGGCGATGAATCATCTGTTGAGATTCCGGAAGAGTCTCTGAT
121 -----+-----+-----+-----+-----+-----+-----+-----+ 180
GACCCGGGTTGGTCAGTGACCGCTACTTAGACAACTCTAAGGCCTCTCAGAGACTA
W A Q P V T G D E S S V E I P E E S L I -
CATCGCTAAAACACCACTTGGCTAACGTGCCATGGCTAACGAGATTGTTAACCAACA
181 -----+-----+-----+-----+-----+-----+-----+-----+ 240
GTAGCGACTTTGTTGAAACCGATTGACCGTACCGATTCTCTAACGCAATTGGTTGT
I A E N T T L A N V A M A K R F V N Q H -
CTTGTGCGGTTCTCACTTGGTTGAAGCTTGTACTTGGTTGTTGAAAGAGGTTCTT
241 -----+-----+-----+-----+-----+-----+-----+-----+ 300
GAACACGCCAACAGAGTGAACCAACTTCGAAACATGAACCAACACCAACTTCTCCAAAGAA
L C G S H L V E A L Y L V C G E R G F F -
CTACACTCCTAACGGAAAAGAGAGGTATCGTTGAACAAATGTTGACTTCTATCTGTTCTT
301 -----+-----+-----+-----+-----+-----+-----+-----+ 360
GATGTGAGGATTCCCTTTCTCCATAGCAACTGTTACAACATGAAGATAGACAAGAAA
Y T P K E K R G I V E Q C C T S I C S L -
GTACCAATTGGAAAACACTGTGGTTAGACGCAGCCCCCAGGCTCTAGA
361 -----+-----+-----+-----+-----+-----+-----+ 409
CATGGTTAACCTTTGATGACACCAATCTGCGTCGGCGTCCGAGATCT
Y Q L E N Y C G * T Q P A G S R -

human insulin
MFalpha leader (ncoI site) - insulin
B(1-30) R A(1-21)

Figure 12

GAATTCCATTCAAGAATAGTCAAACACAAGAAGATTACAAACTATCAATTCATAACAAAT
1 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 60
CTTAAGGTAAGTTCTTATCAAGTTGTTCTTCTAATGTTGATAGTTAAAGTATGTGTTA

N S I Q E * F K Q E D Y K L S I S Y T I -

ATAAACGATTAAAAGAATGAGATTCCTTCAATTTTACTGCAGTTTATTGCAGCATC
61 -----+-----+-----+-----+-----+-----+-----+-----+ 120
TATTTGCTAATTTCTTACTCTAAAGGAAGTTAAAATGACGTCAAAATAAGCGTCGTAG

* T I K R M R F P S I F T A V L F A A S -

CTCCGCATTAGCTGCTCCAGTCAACACTACAAACAGAAGATGAAACGGCACAAATTCCGGC
121 -----+-----+-----+-----+-----+-----+-----+-----+ 180
GAGGCGTAATCGACGAGGTCAAGTTGATGTTGCTTCTACTTGCCGTTTAAGGCCG

S A L A A P V N T T T E D E T A Q I P A -

TGAAGCTGTCATCGGTTACTCAGATTAGAAGGGGATTCGATGTTGCTTTGCCATT
181 -----+-----+-----+-----+-----+-----+-----+-----+ 240
ACTTCGACAGTAGCCAATGAGTCTAAATCTTCCCCTAAAGCTACAACGACAAAACGGTAA

E A V I G Y S D L E G D F D V A V L P F -

TTCCAACAGCACAAATAACGGGTTATTGTTATAAAATACTACTATTGCCAGCATTGCTGC
241 -----+-----+-----+-----+-----+-----+-----+-----+ 300
AAGGTTGTCGTGTTATTGCCAATAACAAATATTATGATGATAACGGTCGTAACGACG

S N S T N N G L L F I N T T I A S I A A -

TAAAGAAGAAGGGGTATCCATGGCTAACGAGATTGTTAACCAACACTGTGCGGTTCCCA
301 -----+-----+-----+-----+-----+-----+-----+-----+ 360
ATTCTTCTTCCCCATAgTACCGATTCTCTAACGCAATTGGTTGTGAAACACGCCAAGGGT

K E E G V S M A K R F V N Q H L C G S H -

CTTGGTTGAAGCTTGTACTTGGTTGTTGAAAGAGGTTCTACACTCCAAAGAC
361 -----+-----+-----+-----+-----+-----+-----+-----+ 420
GAACCAACTTCGAAACATGAACCAAACACCACCTTCTCAAAGAAGATGTGAGGTTCTG

L V E A L Y L V C G E R G F F Y T P K T -

TAGAGGTATCGTTGAACAATGTTGACTTCTATCTGTTCTTGTACCAATTGGAAAAC
421 -----+-----+-----+-----+-----+-----+-----+-----+ 480
ATCTCCATAGCAACTTGTACAACATGAAGATAGACAAGAACATGGTTAACCTTTGAT

R G I V E Q C C T S I C S L Y Q L E N Y -

CTGCAACTAGACGCAGCCCGCAGGCTCTAGA
481 -----+-----+-----+-----+-----+-----+-----+-----+ 511
GACGTTGATCTGCGTCGGCGTCCGAGATCT

C N * T Q P A G S R -

human insulin
MFalpha leader (ncoI site) - MI5
B(1-29) SDDAK A(1-21)

Figure 13

ATCGAATTCCATTCAAGAATAGTTCAAACAAAGAAGATTACAAACTATCAATTCATACAC
1 -----+-----+-----+-----+-----+-----+-----+-----+ 60
TAGCTTAAGGTAAGTCTTATCAAGTTGTTCTAATGTTGATAGTAAAGTATGTG
S N S I Q E * F K Q E D Y K L S I S Y T -
AATATAAACGATTAAAAGAATGAGATTCCTTCAGTTACTGCAGTTATTCCGCAGC
61 -----+-----+-----+-----+-----+-----+-----+ 120
TTATATTTGCTAATTTCTTACTCTAAAGGAAGTTAAAATGACGTAAAATAAGCGTCG
I * T I K R M R F P S I F T A V L F A A -
ATCCTCCGCATTAGCTGCTCCAGTCACACTAACAGAAGATGAAACGGCACAAATTCC
121 -----+-----+-----+-----+-----+-----+-----+ 180
TAGGAGGCGTAATCGACGAGGTCAAGTTGATGTTCTACTTTGCCGTGTTAAGG
S S A L A A P V N T T T E D E T A Q I P -
GGCTGAAGCTGTCATCGGTTACTCAGATTTAGAAGGGGATTCGATGTTGCTGTTGCC
181 -----+-----+-----+-----+-----+-----+-----+ 240
CCGACTTCGACAGTAGCCAATGAGTCTAAATCTTCCCCTAAAGCTACAACGACAAAACGG
A E A V I G Y S D L E G D F D V A V L P -
ATTTCACACAGCACAAATAACGGGTATTGTTATAAAATACTACTATTGCCAGCATTC
241 -----+-----+-----+-----+-----+-----+-----+ 300
TAAAAGGTTGTCGTGTTATTGCCAATAACAAATATTATGATGATAACGGTCGTAACG
F S N S T N N G L L F I N T T I A S I A -
TGCTAAAGAAGAAGGGTATCCATGGCTaagagaTTCGTTAACCAACACTTGTGCCGTTC
301 -----+-----+-----+-----+-----+-----+-----+ 360
ACGATTCTTCTTCCCCATAgGTACCGAttctctAAGCAATTGGTTGTGAACACGCCAAG
A K E E G V S M A K R F V N Q H L C G S -
CCACTTGGTTGAAGCTTGTACTTGGTTGCCGTGAAAGAGGTTCTTCTACACTCCTAA
361 -----+-----+-----+-----+-----+-----+-----+ 420
GGTGAACCAACTTCGAAACATGAACCAAACGCCACTTCTCCAAAGAAGATGTGAGGATT
H L V E A L Y L V C G E R G F F Y T P K -
GtctgacgatgctaaggGTATTGTCGAGCAATGCTGTACCTCCATCTGCTCCTTGTACCA
421 -----+-----+-----+-----+-----+-----+-----+ 480
CagactgctacgattcCCATAACAGCTCGTTACGACATGGAGGTAGACGAGGAACATGGT
S D D A K G I V E Q C C T S I C S L Y Q -
ATTGGAAAACACTGCAACTAGACGCAGCCGCAGGCTCTAGA
481 -----+-----+-----+-----+-----+ 523
TAACCTTTGATGACGTTGATCTGCGTCGGCGTCCGAGATCT
L E N Y C N * T Q P A G S R -

human insulin
MFalpha leader (ncoI site) - insulin
B(1-30) R A(1-21)
N-terminal extension EEAEEA

Figure 14

GAATTCCATTCAAGAATAGTTCAAACAAAGAAGATTACAAACTATCAATTCATACACAAT
1 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 60
CTTAAGGTAAGTTCTTATCAAGTTGTTCTTCTAATGTTGATAGTTAAAGTATGTGTTA

N S I Q E * F K Q E D Y K L S I S Y T I -

ATAAAACGATTAAAAGAATGAGATTCTTCAATTTTACTGCAGTTTATTGCAGCAGCATC
61 -----+-----+-----+-----+-----+-----+-----+-----+ 120
TATTTGCTAATTTCTTACTCTAAAGGAAGTTAAAATGACGTCAAAATAAGCGTCGTAG

* T I K R M R F P S I F T A V L F A A S -

CTCCGCATTAGCTGCTCCAGTCAACACTACAACAGAACAGATGAAACGGCACAAATTCCGGC
121 -----+-----+-----+-----+-----+-----+-----+-----+ 180
GAGGCGTAATCGACGAGGTAGTTGATGTTGTCTTCTACTTGCCGTTTAAGGCCG

S A L A A P V N T T T E D E T A Q I P A -

TGAAGCTGTCATCGGTTACTCAGATTAGAAGGGGATTTCGATGTTGCTGTTGCCATT
181 -----+-----+-----+-----+-----+-----+-----+-----+ 240
ACTTCGACAGTAGCCAATGAGTCTAAATCTCCCCTAAAGCTACAACGACAAAACGGTAA

E A V I G Y S D L E G D F D V A V L P F -

TTCCAACAGCACAAATAACGGGTTATTGTTATAAATACTACTATTGCCAGCATTGCTGC
241 -----+-----+-----+-----+-----+-----+-----+-----+ 300
AAGGTTGTCGTGTTATTGCCAATAACAAATATTATGATGATAACGGTCGTACGACG

S N S T N N G L L F I N T T I A S I A A -

TAAAGAAGAAGGGTATcCATGGCTAACAGAGAGAACAGCTGAAGCTAGATTCTG
301 -----+-----+-----+-----+-----+-----+-----+-----+ 360
ATTCTCTCTCCCCATAgGTACCGATTCTCTCTCGACTTCGACTTCGATCTAACGCA

K E E G V S M A K R E E A E A E A R F V -

TAACCAACACTTGTGCGGTTCCCACTGGTTGAAGCTTGTACTTGGTTGTGGTAAAG
361 -----+-----+-----+-----+-----+-----+-----+-----+ 420
ATTGGTTGTGAACACGCCAAGGGTGAACCAACTTCGAAACATGAACCAAACACCACCTTC

N Q H L C G S H L V E A L Y L V C G E R -

AGGTTTCTTCTACACTCCAAAGACTAGAGGTATCGTTGAACAATGTTGTACTTCTATCTG
421 -----+-----+-----+-----+-----+-----+-----+-----+ 480
TCCAAAGAAGATGTGAGGTTCTGATCTCCATAGCAACTTGTACAACATGAAGATAGAC

G F F Y T P K T R G I V E Q C C T S I C -

TTCTTTGTACCAATTGGAAAACTACTGCAACTAGACGCAGCCCCGAGGCTCTAGA
481 -----+-----+-----+-----+-----+-----+-----+-----+ 535
AAGAAAACATGGTTAACCTTTGATGACGTTGATCTGCGTCGGCGTCCGAGATCT

S L Y Q L E N Y C N * T Q P A G S R -

Figure 15

human insulin
 MFalpha1 leader (ncoI site) - MI5
 B(1-30) R A(1-21)
 N-terminal extension EEAEEAE

60

1 GAATTCCATTCAAGAATAGTCATAACAAAGAAGATTACAACACTATCAATTCTACACAAAT
 CTTAAGGTAAGTCTTATCAAGTTGTTCTTAATGTTGATAGTTAAAGTATGTGTTA
 N S I Q E * F K Q E D Y K L S I S Y T I -
 61 ATAAACGATTAAAAGAATGAGATTCTTCAATTTCAGTTACTGCAGTTTATCGCAGCATC
 TATTTGCTAATTTCTTACTCTAAAGGAAGTAAAAATGACGTCAAATAAGCGTCGTAG
 * T I K R M R F P S I F T A V L F A A S -
 121 CTCCGCATTAGCTGCTCCAGTCAACACTACAACAGAAGATGAAACGGCACAAATTCCGGC
 GAGGCGTAATCGACGAGGTCAAGTTGATGTTGCTTACTTTGCCGTGTTAAGGCGC 180
 181 TGAAGCTGTCATCGGTTACTCAGATTAGAAGGGATTTCGATGTTGCTGTTGCCATT
 ACTTCGACAGTAGCCAATGAGTCTAAATCTCCCCTAAAGCTACAACGACAAAACGGTAA 240
 E A V I G Y S D L E G D F D V A V L P F -
 241 TTCCAACAGCACAAATAACGGGTTATTGTTATAAAATACTACTATTGCCAGCATTGCTGC
 AAGGTTGTCGTGTTATTGCCAATAACAAATATTATGATGATAACGGTCGTACGAGC 300
 S N S T N N G L L F I N T T I A S I A A -
 TAAAGAAGAAGGGTATCCATGGCTAAGAGAGAAGAAGCTGAAGCTGAAGCTGAAAGATT
 301 ATTTCTTCTCCCCATAGTACCGATTCTCTCTTCTCGACTTCGACTTCGACTTTCTAA 360
 K E E G V S M A K R E E A E A E A E R F -
 361 CGTTAACCAACACTGTGCGGTTCCACTGGTTGAAGCTTGACTTGGTTGGTGA
 GCAATTGGTTGTGAACACGCCAACGGTGAACCAACTCGAAACATGAACCAACACCACT 420
 V N Q H L C G S H L V E A L Y L V C G E -
 AAGAGGTTCTTCTACACTCCAAAGACTAGAGGTATCGTTGAACAATGTTGACTTCTAT
 421 TTCTCCAAAGAAGATGTGAGGTTCTGATCTCCATAGCAACTGTTACAACATGAAGATA 480
 R G F F Y T P K T R G I V E Q C C T S I -
 CTGTTCTTGTACCAATTGGAAAACTACTGCAACTAGACGCAGCCCGAGGCTCTAGA
 481 GACAAGAAACATGGTTAACCTTTGATGACGTTGATCTGCGTCGGCGTCCGAGATCT 538
 C S L Y Q L E N Y C N * T Q P A G S R -
 .